# Farid Haploidentical Stem Cell Transplantation for Pediatric Leukemia: A Hypothesis-Driven Approach to Ethical and Effective Treatment

**Prof. Dr. Md. Faridul Islam Chowdhury**
Neuroscientist, Neurosurgeon, and Theoretical Cosmologist
Tanfarid Vision Research Institute, Bogura, Bangladesh

Email: dr_faridul@yahoo.com

***Disclaimer: This protocol is investigational and must only be applied by qualified, licensed physicians***

# Abstract

**Background:** Allogeneic hematopoietic stem-cell transplantation (HSCT) is the only curative option for high-risk pediatric acute leukemia (AL). Conventional myeloablative regimens cause severe long-term complications, while reduced-toxicity approaches often increase relapse risk.

**Objective:** We propose a novel protocol using parent-derived, G-CSF-mobilized haploidentical peripheral blood stem cells (PBSCs), purified by CD34+ selection and αβ-T-cell depletion, with minimal conditioning to achieve stable engraftment and graft-versus-leukemia (GVL) effects while minimizing transplant-related mortality (TRM).

**Methods:** Parental donors received G-CSF, with PBSCs harvested at peak CD34+ levels. Products were CD34+ enriched and αβ-T-cell depleted. Pediatric recipients underwent immunosuppression-focused conditioning (treosulfan ± fludarabine) without myeloablation. Post-transplant cyclophosphamide (PTCy) was used for graft-versus-host disease (GVHD) prophylaxis.

**Results:** Three infants (8–14 months) with relapsed acute myeloid leukemia (AML) were treated compassionately. Median neutrophil engraftment was 11 days, with 100% donor chimerism by day +21. GVHD was mild (grades 0–II).

**Conclusion:** This haploidentical protocol shows feasibility, rapid engraftment, and low GVHD in high-risk infants. It supports a hypothesis of ordered, non-stochastic stem cell homing, reducing reliance on cytotoxic ablation. Further validation via single-cell genomics and biophysical modeling is needed, potentially linking transplantation to thermodynamic principles of biological order.

# 1. Introduction: Ethical Need for Low-Toxicity HSCT

Allogeneic HSCT cures high-risk pediatric leukemia but often at the cost of lifelong morbidity from myeloablative conditioning, including endocrine dysfunction, neurocognitive decline, infertility, and secondary malignancies. The ethical challenge is to preserve curative potential while minimizing harm. Haploidentical transplantation with parental donors, enhanced by αβ-T-cell depletion and PTCy, has reduced GVHD risks. The next step is minimizing pre-transplant toxicity by leveraging stem cell biology.

# 2. Hypothesis: Engraftment as an Ordered Process

Traditional HSCT assumes engraftment requires marrow space created by myeloablation and host hematopoiesis destruction. We propose:

- Stem cell homing and niche integration are deterministic, ordered processes.
- Immunosuppression alone enables CD34+ cell engraftment without extensive ablation.
- Cytotoxicity can be minimized, shifting HSCT from destruction to facilitation.

This aligns with the thermodynamic autorunner principle (τ), where biological systems optimize minimal entropy and maximal recognition efficiency, reflecting cosmological order in the Tanfarid Quantum Thermodynamic Universe (TQTU) framework [1, 2].

# 3. Clinical Protocol

## 3.1 Donor Mobilization and Collection

- **Donor:** Haploidentical parent.
- **Mobilization:** G-CSF 10 μg/kg/day, days -5 to -1.
- **Collection:** Apheresis at CD34+ peak (≥$8 \times 10^6$ cells/kg recipient weight).
- **Processing:** CD34+ enrichment and αβ-T-cell depletion (CliniMACS).

## 3.2 Minimal Conditioning

- Treosulfan: 30 g/m² (days -3 to -2).
- Fludarabine: 150 mg/m² (days -5 to -3, optional).
- No total body irradiation or additional alkylators.
- **Goal:** Immunosuppression without organ toxicity.

## 3.3 Infusion and Post-Transplant Care

- **Day 0:** Stem cell infusion.
- **GVHD Prophylaxis:** PTCy 50 mg/kg (days +3, +4).

- **Supportive Care:** G-CSF from day +5; antimicrobial prophylaxis.

# 4. Pilot Data: Compassionate-Use Cohort

| Patient | Age (months) | Diagnosis | Conditioning | Neutrophil Engraftment (days) | D+21 Donor Chimerism | GVHD (Max Grade) |
|---|---|---|---|---|---|---|
| 1 | 14 | Relapsed AML | Treosulfan + Fludarabine | 10 | 100% | I |
| 2 | 8 | Relapsed AML | Treosulfan only | 12 | 100% | 0 |
| 3 | 11 | Relapsed AML | Treosulfan + Fludarabine | 11 | 100% | II |

- **Median Neutrophil Recovery:** 11 days.
- **Chimerism:** 100% donor by day +21.
- **GVHD:** Grades 0–II, no severe cases.

# 5. Discussion: Redefining Engraftment

These results suggest high-intensity cytotoxicity is not essential for engraftment. Ordered biophysical mechanisms likely drive success:

- Chemokine gradients (CXCL12-CXCR4).
- Adhesion interactions (VLA-4/VCAM-1).
- Niche-specific recognition signals.

This challenges stochastic clearance models, aligning with thermodynamic integration ($\tau$ principle, TQTU) [1]. The approach preserves GVL effects while reducing toxicity, enhancing ethical standards.

# 6. Future Directions

- **Molecular Analysis:** Single-cell RNA sequencing to map host-donor interactions.
- **Modeling:** Bioinformatics to simulate homing vs. stochastic clearance.
- **Predictive Index:** Develop an Engraftment Prediction Index using CD34+ dose, purity, and recognition biomarkers.
- **Ethical Advances:** Explore non-chemotherapeutic immunosuppression (e.g., biologics).

# 7. Conclusion

This pilot validates a haploidentical PBSC protocol for pediatric AML, emphasizing ordered stem cell homing over ablation. Integrating clinical and thermodynamic perspectives, it suggests

engraftment follows universal principles of order, with potential to transform transplantation and biological sciences.

# References


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The described treatment may only be performed by **authorized, licensed physicians** with demonstrated expertise in immunology, medical sciences, and hematopoietic stem cell transplantation. **Unauthorized use by unqualified individuals is strictly prohibited** and may cause serious harm.

For safe and ethical application, implementation by a **multidisciplinary team** is strongly recommended — including a pediatrician, hematologist, immunologist, and transplantation specialists.

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